Adult Leukemia Following Diagnostic X-Rays?

(Review of report by Bross, Ball, and Falen on a tri-state leukemia survey)

JOHN D. BOICE, SCD AND CHARLES E. LAND, PHD

Introduction

Bross, et al,[1] have developed a "new statistical methodology" to re-analyze data from a tri-state leukemia study.[2,3] They report adult leukemia and heart disease to be related to diagnostic x-ray skin doses of between 0.1 and 10 rad, and conclude that previous risk estimates underestimate radiation hazards by a factor of 10. Although we agree that medical x-rays should not be performed without reason and that certain host factors may increase susceptibility to radiation effects, we feel that the conclusions of the article (e.g., that a *dose-effect* curve was demonstrated in the one rad range) are not justified by the analysis or data reported.

The statistical model used by Bross, et al, appears unsuited for analysis of the tri-state data. Precise estimates of "risk" are obtained only by incorrectly treating estimated values as known constants, and results are not consistent with a large body of data from epidemiologic studies. Furthermore, to our knowledge the "new statistical methodology" has never been presented in a journal devoted to statistical methods and has not, therefore, received the kind of critical peer review required before such a technique can be accepted as useful and valid.

In addition, no radiation dosimetry was performed, and the casual way in which radiation doses were assigned ignores factors that could radically change the shape of any dose-effect relationship.

Conventional case-control analyses do demonstrate an association between diagnostic x-ray and leukemia, but not necessarily heart disease. The excessive x-rays reported by patients, however, were possibly administered for pre-leukemic states or early stages of leukemia. The excess heart disease, if real, is also likely an artifact related to leukemia patients receiving more intense clinical examinations than population controls. Alternatively, the association between leukemia and diagnostic x-ray may be entirely due to a few individuals who received massive diagnostic radiation exposures.

Finally, Bross, et al, have failed to review the literature on similar studies on adult leukemia. These studies are indispensable to the interpretation of the results, and are briefly summarized.

Literature Review

Adult Leukemia Studies

Studies linking diagnostic radiation with adult non-lymphocytic leukemia have been reported in England,[4] New Zealand,[5] and the United States.[3] These studies, including the previous tri-state survey analysis, are summarized in Table 1. Each study reported an association in adults between diagnostic x-rays and myeloid leukemia, but not lymphatic leukemia. Myeloid leukemia is the type found most frequently following high-dose radiation exposures.[6,7] It is also noteworthy that the reported associations were strongest for diagnostic x-ray exposures of active bone marrow sites, i.e., exposures of the chest and abdomen as opposed to peripheral sites. However, these authors were particularly cautious in interpreting their data, concluding that oniy a small percentage of leukemia in adults might be associated with diagnostic x-rays. The risk of myeloid leukemia appeared to be concentrated among those receiving unusually large numbers of examinations (and only in males in the tri-state survey). It seems plausible, then, that the observed association between myeloid leukemia and diagnostic x-rays is entirely due to a few individuals who received massive exposures more similar to radiotherapy for benign diseases than to the usual experience with diagnostic x-rays.[8]

Of particular interest is Stewart's retraction[9] of an earlier report[4] that about 8 percent of adult myeloid leukemia in England had been caused by x-ray examinations of the chest and abdomen. Re-interpreting her study, Stewart concluded that pre-leukemic conditions were manifested by a height-

From the Environmental Epidemiology Branch, National Cancer Institute. Address reprint requests to Dr. John D. Boice, Environmental epidemiology Branch, National Cancer Institute, Room 3C-07, Landow Building, Bethesda, MD 20014. This paper, submitted to the Journal November 1, 1978, was accepted for publication November 7, 1978.

TABLE 1—Case-Control Studies of Adult Leukemia and Diagnostic X-rays

Study	Cases	Controls	Non-lymphatic Leukemia Popn.	PAR%*	Comments
1. Stewart, et al,[4] 1962	531 male and 491 female leukemias over age 20 diagnosed between 1958 and 1960 in England	974 healthy controls selected from population registries	215 males, 296 females	8% for non-lymphatic leukemia	Risk reported as 1 leukemia death per 46,000 x-rays. Author later retracted her finding and suggested that the observed leukemia excess was an artifact.[9]
2. Gunz and Atkinson,[5] 1964	337 male and 253 female leukemias of all ages diagnosed between 1958 and 1961 in New Zealand	590 hospital controls	No attempt made to subdivide acute leukemia according to cellular type	Less than 1% for all leukemias	Inconclusive. Excess risk due entirely to 2 or 3 patients with massive numbers of x-rays. With these high exposure patients excluded, no association seen. Dosimetry attempted.
3. Gibson, et al,[3] 1972	850 male and 564 female leukemias over age 15 diagnosed between 1959 and 1962 in tri-state survey (NY, MD, MN)	668 male and 702 female controls selected from a sample of households	339 males, 251 females	4.8% for chronic myeloid leukemia in males attributed to exposure to 21 + x-rays (8.8% for 11 + x-rays)	No risk in females. Authors concluded that only a small proportion of leukemia is attributable to diagnostic x-rays and that males may be more radiosensitive than females for leukemia.

*Population attributable risk per cent.[38] The estimated proportion of leukemia in the general population that may be attributable to diagnostic x-rays.

ened sensitivity to infections, which accounted for the unusually high number of x-rays performed during the five-year period before the diagnosis of leukemia. If true, the association between diagnostic x-rays and leukemia in adults would be indirect rather than causal.

Radiation-induced Leukemia Studies

Ionizing radiation is perhaps the most extensively studied carcinogen.[10,11] Of particular note are the studies of atomic bomb survivors[12] and British radiotherapy patients treated for ankylosing spondylitis.[7,13,14] In both of these cohort studies, large populations of exposed individuals were successfully followed for many years and disease occurrence determined. Great attention was paid to the estimation of radiation doses to body organs. The risk of leukemia at high doses (50+ rad) is well established but the risk at lower doses is uncertain due to sampling variability at low doses, and due to uncertainty about the shape of the dose-response function to use for extrapolation of high-dose risk estimates. These data have also been interpreted as suggesting that the excess risk per rad for gamma rays is less at low doses than at higher dose levels.[15] The dose-effect relationship is consistent with linearity for both the A-bomb survivors and the British patients, but more complex functions suggested by experimental studies are also compatible with the data.

The association of leukemia and low dose prenatal x-ray exposures has been known for years,[16,17] and it appears that the developing fetus may be particularly sensitive to ionizing radiation. Therapeutic irradiation for benign menstrual disorders appears to increase leukemia risk, whereas higher dose therapy for cervical cancer does not.[18] An association between radiation and leukemia has also been reported in patients given thorotrast, in children irradiated for tinea capitis, and in children irradiated for enlarged thymus glands.[10] An excess risk of leukemia among radiologists who practiced during the 1920s and 1930s has been observed in the U.S.[19] but not in England.[20] Patients treated with radioactive iodine-131 for hyperthyroidism have not shown an increased risk for leukemia when compared with surgically treated patients.[21] No excess leukemia risk was reported in 6,560 Army x-ray technicians who were followed for 29 years.[22] A study of 1,047 tuberculosis patients who received an average of 102 fluoroscopic chest examinations between 1930-1954 also failed to detect a leukemia excess (2 observed and 1.2 expected).[23,24] In the latter study, the diagnostic x-ray exposures (about l000R to the chest) were much larger than those in the tri-state survey; however, because the bone marrow dose was not large, the failure to detect an excess leukemia risk was predictable, assuming conventional estimates of risk are valid.[10] According to the estimates of Bross, et al, however, a large excess should have been detected with high probability in a sample of this size.

Referenced Studies

The Hanford study by Mancuso, et al,[25] of nuclear workers was referenced by Bross, et al, as confirming their conclusions, but this too is a controversial study with respect to both statistical analysis and interpretation. Others evaluating the same data have reached different conclusions.[26-28] No association was seen between myeloid leukemia and radiation, contrary to the implication by Bross, et al, but an increased risk was suggested for pancreatic cancer and multiple myeloma, which are not usually prominent among diseases correlated with radiation exposure. The Hanford study has received further criticism,[29,30] and two of the authors of the original analysis have subsequently stated that future work is needed to determine whether there is a cancer hazard for workers in the nuclear industry.[31]

The tri-state prenatal x-ray studies,[32,33] referenced by Bross, et al, have also been questioned,[34-37] and most would like to see the data on susceptibility confirmed in other series before drawing conclusions from the re-analysis of a previous study.

Detailed Critique

Introduction

It should be emphasized that the data with regard to leukemia risk have been published in detail by Gibson, et al, in 1972.[3] A dose-effect relationship was suggested between the risk of non-lymphatic leukemia and the number of x-ray films reported. To determine skin exposures (the Bross, et al, "dose"), the number of examinations were simply multiplied by published values of skin exposure (in roentgens) per examination. This simple transformation of scale adds very little to the previous analysis; risk is seen to increase with skin exposure (not bone marrow dose) whereas before it was found to increase with number of x-ray films.

Potential Biases

Before accepting a causal association between diagnostic x-ray exposure and adult non-lymphatic leukemia, it is important to consider alternative explanations as well as possible study biases.

1. *Confounding Factors.* Stewart[9] has suggested that pre-leukemia conditions led to a heightened sensitivity to infections that may be responsible for x-rays performed during the five-year period prior to the diagnosis of leukemia. Several years earlier, MacMahon[38] (p. 243) raised this possibility in discussing the potential difficulties in distinguishing between past events causally related to leukemia from events consequent to the disease. Thus, it is unclear whether x-ray exposures reported by the patients were given for antecedent manifestations of early symptoms of the disease. In the tri-state survey, one-half of the total x-ray exposures occurred within five years of the leukemia diagnoses, and the Stewart or MacMahon caveat may also apply.

Furthermore, it seems possible that underlying conditions that required multiple chest and abdominal x-rays (e.g., greater than *41)* may contribute in some way to the subsequent development of leukemia.

2. *Observational Bias.* When an interviewer knows the leukemia status of the respondent he may push harder for a response to the radiation questions among the leukemia cases. Although the interviews began in a blind fashion as Bross, et al, state, the leukemia status of 70 percent of the cases was discovered during the interview.[2]

3. *Ascertainment of Exposure.* Graham, et al,[2] indicated that about 74 percent of the x-rays ascertained were not mentioned in the interview, but were determined by searching physician and hospital records. It is likely that the total exposure experience of the population was underestimated. A bias would result, however, if the determination of exposure were greater for one group than the other. It seems possible that patients hospitalized for leukemia might very well have had more complete and more readily available current and past medical records than population controls not hospitalized. If true, a portion of the excess proportion of x-rays among cases might be explained by differential accessibility to exposure information.

4. *Response Bias.* Only 20 percent of the patients were alive at the time of interview, and relatives had to be interviewed for those cases who had died. The effect of relying on relatives increases the probability of errors but the magnitude is uncertain.

The refusal rate of interview was 3 percent for the cases and 6 percent for the controls. However, an additional 17 percent of the cases were not interviewed for various other reasons versus 2 percent of the controls.[2] The effect of not obtaining information for 20 percent of the cases versus 8 percent of the controls is also unknown.

Another factor that cannot be evaluated is the possible desire of individuals to assign a cause to their illness. By 1960, it was public knowledge that radiation increased the risk of leukemia.[7,16,39] Persons with leukemia or their relatives might have recalled more x-rays and hospitalizations than did controls in an attempt to attribute the leukemia to a known carcinogen. Alternatively, the traumatic experience of leukemia might cause these patients or their families to be more reliable witnesses than population controls.

5. *Missing Data.* The original paper by Gibson, et al,[3] reported 339 male patients with acute and chronic myeloid and monocytic leukemia whereas Bross, et al, have analyzed only 206 "non-lymphatic" cases. The reasons for this selection of cases are not clear.

Statistical Evaluation

Bross, et al, have stressed a new statistical methodology developed for the analysis of the tri-state data, and it is fitting, therefore, to subject their analysis to close examination. Enough detail is given in Tables B1* and B4, Figure B1, and the text dealing with Table B1 to reconstruct the analysis, but only for men over 65 years of age.

The first step was to see if the parameter values in the text and in Table B4, when applied to the model of Figure B1, gave the expected values in Table B1. Surprisingly they did not, but could be made to do so with certain modifications. The sampling rate, parameter 3, had to be changed from 1:9000, as given in the text, to 1:3000 as given by Gibson, et al.[3] More serious, the value of parameter 1 (the number of men in the irradiated category) had to be modified for each of the dose classes, as was obvious from an examination of the model. The given value of the first parameter, 257,441, had to be replaced by dose-specific values 43,917, 41,922, 29,949, 17,963, and 3,990 for the dose categories corresponding to <1, 1-5, 5-10, 10-20, and 20+ rad, respectively. These numbers add to only 53.5 per cent of 257,441, raising the question of just what the given value for parameter 1 does represent. It is appropriate to note that the unmentioned dose-specific numbers are also parameters, and to ask how they were obtained. It is difficult to imagine that they could

*A "B" preceding a Table or Figure number refers to the Bross, et al, Table or Figure.

have been obtained otherwise than from the interview data. The evaluation of the obtained chi-square should take into account these 5 extra parameters not mentioned by Bross, et al, each of which removed 1 degree of freedom.

It is interesting that 257,441 was given in reference 40 as the number of men age 65 years or older who were exposed to O-5 rad. In that same reference the sampling rate was given as 1.565, the value in the present paper of parameter 4, the "age adjustment factor" for ages 65+. All this suggests, at the very least, a certain carelessness and disregard for detail in the present paper and in reference 40.

The difference between the numbers of leukemias expected according to parameter 2 (the assumed population rate for leukemia) and those observed in the lower dose categories forms the basis for the authors' conclusion that many leukemia (and heart disease) cases have been caused by very low doses of radiation. The given value of the population rate for leukemia, 14.23 per 100,000, is very low compared to rates obtained from the age-specific Connecticut tumor registry data for 1968-1972[41] and standardized to the age distribution for the over-65 male population of upper New York State as of 1960.[42] These rates (per 100,000) are 66.04 for all leukemia and 34.65 for myeloid and monocytic leukemia. Leukemia rates have not increased enough since the tri-state survey to account for the discrepancy between these rates and the given value of parameter 2; the standardized Connecticut rate for leukemia and aleukemia for 1960-1962 was 56.5 per 100,000.[41] If, as it appears, the value of parameter 2 was developed at least partly from the data, this should also be reflected in the degrees of freedom.

Parameters 4 and 5 do not appear to be simple functions of the data in Table B1. The "age adjustment factor" presumably refers to a discrepancy between the age distributions of the 1:3000 random sample and the underlying population,[2,3] and should therefore correspond to the ratio of the number of non-leukemia subjects in Table B1 to the number of men in the population, times the sampling rate. As computed from Table B1 this ratio is 1.48 = 68/(.535 x 257,441/3000), not 1.565. However, there may be an additional factor to reflect incompleteness of interview. Parameter 5, the "probability of heart disease", is given as .201, which is less than 19/68 = .279, the proportion of heart disease among the non-leukemia subjects, and 9/43 = .209, the proportion among those with less than 5 rad.

In view of the above discussion, the model given by Bross, et al, should be modified to make its dose dependence more explicit. Ignoring the age variable x_3, since only the data for ages 65 and older can be analyzed in detail, and adding a new variable x_4, to denote dose class (1 = less than 1 rad, . . ., 5 = 20+ rad), we have

$$E(x_2, x_3, x_4) = N(x_4)[1 - F(x_4) P_0(x_2, x_3) + F(x_4) P_1(x_2, x_3)](AS)^{1+x_2},$$

where P_0 and P_1 are as given in the model. There are 14 parameters whose derivations appear to depend on the data of Table B1: N(1),..., N(5), F(1),..., F(5), R_H, R_L, H_0 and A. In addition, it seems undeniable that the value of the assumed population leukemia rate, L_0, also reflects sample data. This leaves 5 degrees of freedom for the overall chi-square value (5.85) for Table B1, which indeed indicates an acceptable fit of the model to the data ($p > .30$). On the other hand, assuming the same approach was followed for Tables B2 and B3, the overall chi-square values of 22.99 (with 5 degrees of freedom or, if R_H and R_L are assumed to be the same as in Table B1, 7 degrees of freedom and $p < .002$) for Table B2 and 8.37 (with 1 or 3 degrees of freedom and $p < .04$) for Table B3 indicate a much less close agreement of model to data.

As described by Bross, et al, the fitting procedure used to estimate the parameters F(1),... ,F(5), the "proportions affected" in each of the 5 dose classes, assumes that the other 10 parameters are fixed. The confidence limits in Table B4 and Figure B2, therefore, are misleadingly precise because they ignore the random nature of the other 10 parameter estimates. The effect on the apparent precision of the fitted parameter estimates obtained by assuming other estimated parameter values to be known is illustrated in Table 2. In the 3 analyses shown, parameters F(1),..., F(5) were fitted by minimum chi-square, assuming the values of parameters N(1),... N(5), A, and L_0 to be fixed. In the first analysis, in which parameters H_0, R_L, and R_H were also kept fixed, the estimates of F(l),..., F(5) were close to those given by Bross, et al, in Table B4, with a similar value of χ^2, and the estimated standard deviations were small relative to their corresponding parameter estimates. In the second analysis R_L and R_H were no longer fixed but were obtained by fitting. A smaller value of χ^2 was obtained, the estimates of all the fitted parameters were different than in the first analysis, and the standard deviations of the estimated parameters were increased to the extent that F(1), F(2) and F(3) were not significantly different from zero. In the third analysis, H_0 also was included among the fitted parameters. These estimates "fitted the facts" even better, as measured by χ^2, but this time none of the estimated "proportions affected" were significantly greater than zero. Taking the data-dependence of the remaining parameters into account would have a similar effect on the standard deviations of the fitted estimates.

The above example illustrates one reason why the "new statistical method" of Bross, et al, has not been used by other investigators: it does not produce estimates of usable precision. The model is so complicated and so richly parameterized that an extremely wide range of parameter values is consistent with these data. The Bross, et al, model assumes that the dose-response curve is determined by the composition of the general population with respect to subgroups of varying susceptibility to radiation damage and not, as in more conventional dose-response models,[44-47] by the assumed physical mechanism of radiation damage to cellular material. Thus, the "proportion affected" in one dose class has no necessary relationship to that in another dose class, and 5 parameters (F(l),..., F(5)) are needed to express the dose dependence of risk, rather than 1 or 2. Fixing the values of the other parameters in the model artificially improves precision to the level of, say, conventional estimates of the leukemia rates in each of the 5 dose classes. However, the method incorrectly assumes that the values of the other parameters are known, when they are, in fact, estimated from the data.

Part of the interpretation by Bross, et al, of their analy-

TABLE 2—Analyses of Tri-state Survey Data from Table 1 of Bross, et al,[1] using their Model: Minimum Chi-square Estimates with Estimated Standard Errors, with Different Choices of Fixed and Fitted Parameters

1st Analysis	2nd Analysis	3rd Analysis
Fixed Parameters	*Fixed Parameters*	*Fixed Parameters*
N(1) = 43917	N(1) = 43917	N(1) = 43917
N(2) = 41922	N(2) = 41922	N(2) = 41922
N(3) = 29949	N(3) = 29949	N(3) = 29949
N(4) = 17963	N(4) = 17963	N(4) = 17963
N(5) = 3990	N(5) = 3990	N(5) = 3990
A = 1.565	A = 1.565	A = 1.565
L_O = .0001423	L_O = .0001423	L_O = .0001423
H_O = .201	H_O = .201	*Fitted parameters*
R_L = 10	*Fitted parameters*	H_O = .2608 ± .0338
R_H = 3	R_L = 5.769 ± 2.560	R_L = 6.242 ± 4.047
Fitted parameters	R_H = 2.690 ± 0.342	R_H = 1.928 ± 0.376
F(1) = .0403 ± 0.152	F(1) = .0766 ± .0504	F(1) = .0557 ± .0520
F(2) = .0549 ± .0169	F(2) = .1050 ± .0648	F(2) = .0923 ± .0785
F(3) = .0514 ± .0196	F(3) = .1007 ± .0656	F(3) = .0733 ± .0670
F(4) = .2251 ± .0412	F(4) = .4364 ± .2379	F(4) = .3947 ± .3070
F(5) = .5903 ± .1286	F(5) = 1.0000* ± .5382	F(5) = 1.0000* ± .7638
χ^2 = 5.87	χ^2 = 4.77	χ^2 = 3.85

*The parameters F(1), . . . , F(5) are constrained to be between zero and one.

sis rests on a semantic fiat: the parameters (F(l), . . ., F(5) represent the "proportions affected by radiation." This seems unduly restrictive, since leukemia can be caused by agents other than radiation. No data are presented on populations not exposed to diagnostic x-rays, but the trend of the estimated "proportions affected" suggests that there is little change with dose in the 0-10 rad range (Table B4, Figures B2 and B3). Far from implicating diagnostic x-ray at doses less than one rad, this suggests that the "proportion affected" is not affected very much by x-ray doses less than 10 rad. There appears to be a minimum "proportion affected" that has nothing to do with diagnostic x-ray. When this minimal value has been subtracted, the Bross, et al, analysis suggests that the effects of x-ray doses on the order of one rad are an order of magnitude *less* than would be estimated by linear extrapolation from, say, 40 rad.

The "proportion affected" at 40 rad, for those over age 65, was estimated by Bross, et al, to be 61 per cent, or about 57 per cent plus the estimated "proportion affected" (about 4 per cent) at less than 1 rad. Since no more than 100 per cent of the irradiated population can be affected, it follows from the reported analysis that most of the possible damage, at least as far as leukemia and heart disease are concerned, must be done by the first 40 rad of x-ray dose. In fact, the second and third analyses in Table 2, whose estimates "fit the facts" even better than those calculated by Bross, et al, estimate the "proportion affected" at 40 rad to be 100 per cent, leaving no possibility of additional effects from higher doses. Leukemia incidence has been observed to be many times higher among the Japanese A-bomb survivors exposed to 200 rad or more, than among those exposed to 10-49 rad and to 50-99 rad,[6-12] and much more than 10 times higher than population rates, suggesting a rather profound disagreement between fact and model. The reported instances of radiation-induced heart disease[48-51] have also been at extremely high doses. The model as analyzed by Bross, et al, implies, however, that at very high doses the incidence of radiation-induced heart disease should be no more than three times normal, a rate at which it would be difficult to prove any association with radiation given the small numbers of people exposed to such high doses. The model also implies that the incidence of leukemia must be limited to 10 times the normal rate. This is clearly inconsistent with a large body of experimental and epidemiologic data.

A more conventional, contingency table analysis of the case-control data by dose class yielded statistically significant tests for increasing linear trend in leukemia incidence with increasing dose for ages 65+ and 45-64, but not for ages 15-44 (Table 3). The analysis did not suggest any deviations from linearity.

A similar analysis of the heart disease data, adjusted for case versus control differences,[52-54] found no evidence of an increasing trend in heart disease with increasing dose for ages 65+ and 45-64. There was, however, a suggestion, based on extremely small numbers, of a trend in the youngest group (Table 4).

Finally, 2 x 2 contingency tables were used to test for an association between leukemia and heart disease within age and dose group (Table 5). For ages 65 + and 15-44 there was no evidence of such an association, either for single dose classes or in summary. For ages 45-64 there was evidence of an association, which was strongest among those exposed to the smallest doses. According to the interpretation of Bross, et al, in which leukemia and heart disease are associated because they are both caused by ionizing radiation, the association between them, as measured by the

TABLE 3—Contingency Table Analyses of Leukemia Case-control Data, by Age and Exposure Class

Ages 65+:	Average skin dose (rad)	0.4	2.3	6.7	13.1	39.5	Total
	Leukemia cases	23	28	16	23	11	101
	Controls	22	21	15	8	2	68
	Non-homogeneity: χ^2 (4)* = 8.4, p = .08						
	Trend: Z = 2.50, p = .006						
	Non-linearity: χ^2 (3) = 2.2, p = .53						
Ages 45–64:	Average skin dose (rad)	0.4	2.2	6.8	13.5	31.5	Total
	Leukemia cases	17	24	9	14	10	74
	Controls	54	41	25	16	7	143
	Non-homogeneity: χ^2 (4) = 11.1, p = .03						
	Trend: Z = 2.78, p = .003						
	Non-linearity: χ^2 (3) = 3.4, p = .33						
Ages 15–44:	Average skin dose (rad)	0.7	7.2	13.3			Total
	Leukemia cases	27	2	2			31
	Controls	49	7	6			62
	Non-homogeneity: χ^2 (2) = 0.9, p = .64						
	Trend: Z = −.85, p = .80						
	Non-linearity: χ^2 (1) = 0.2, p = .67						

*Degrees of freedom shown in parentheses

odds ratios in Table 5, should increase with increasing dose. However, the trend is in the opposite direction, raising the possibility of a purely artifactual association.

Radiation-Induced Heart Disease

Very large radiation doses have been related to an increased risk of heart damage in cancer patients treated with thousands of rads.[48–51] However, no excess heart disease has been detected in large groups exposed to lower doses. Among A-bomb survivors,[55] there were 3,706 observed deaths due to circulatory diseases versus 4,141 expected (SMR = 0.89). Among radium dial painters,[56] 60 deaths due to circulatory disease were observed versus 62.0 expected (SMR = 0.97).

A major difficulty in the reported association between heart disease and diagnostic x-rays by Bross, et al, is the ascertainment of heart disease in this case-control study. Concurrent heart disease was included in the analysis, and thus some heart disease was detected at the time of the initial medical examination. Since most controls obviously did not receive extensive medical screening, it seems more plausible that the excess heart disease, if real, is related to closer surveillance and medical screening of leukemia cases at the time of diagnosis or during the evaluation of early manifestations such as anemia, splenomegaly, osteoarticular pain, or hypermetabolic symptoms such as fever, sweats, and weight loss.

A final difficulty is the possibility that some of the reported "heart disease" became apparent because of the leukemia. For example, anemia may aggravate underlying heart

TABLE 4—Contingency Table Analyses of Heart Disease Data, by Age and Skin Dose, Adjusted for Case-control Differences

Ages 65+:	Average dose (rad)	0.4	2.3	6.7	13.1	39.5
	Heart disease: Obs.	14	13	12	14	6
	Exp.*	15.3	17.0	10.5	11.3	4.9
	Non-homogeneity: χ^2 (4)‡ = 3.3, p = .51					
	Trend: Z = 1.24, p = .11					
	Non-linearity: χ^2 (3) = 1.8, p = .61					
Ages 45–64:	Average dose (rad)	0.4	2.2	6.8	13.5	31.5
	Heart disease: Obs.	10	11	11	5	5
	Exp.*	12.2	13.0	6.0	6.6	4.2
	Non-homogeneity: χ^2 (4) = 7.0, p = .14					
	Trend: Z = 0.64, p = .26					
	Non-linearity: χ^2 (3) = 6.6, p = .09					
Ages 15–44:	Average dose (rad)	0.7	7.2	13.3		
	Heart disease: Obs.	3	1	2		
	Exp.*	4.9	0.6	0.5		
	Non-homogeneity: χ^2 (2) = 5.6, p = .06**					
	Trend: Z = 2.33, p = .01**					
	Non-linearity: χ^2 (1) = 0.2, p = .65**					

*Expected value adjusted for case-control differences.[52–54]
**Tests based on extremely small cell frequencies. P-values are unreliable.
‡Degrees of freedom shown in parentheses.

conditions to produce signs of tachycardia, angina pectoris, and congestive heart failure.[57] It is also possible that patients with heart disease would receive more chest x-ray examinations than those without heart disease.

In summary, because the reported association is not consistent with current knowledge on radiation-induced heart damage, because observational bias related to more intense screening of leukemia patients cannot be ruled out, and because a proportion of the reported "heart disease" is probably attributable to anemia and other complications of leukemia, the reported association between heart disease and diagnostic x-ray is likely an artifact.

Dosimetry

Because Bross, et al, claim to be reporting a "dose-response" relationship, it is important to comment on their "dosimetry". No radiation exposures were measured, no x-ray machines evaluated, and no organ dose computed. Bross, et al, simply took published average exposure values in the United States in 1964[58, 59] and multiplied these values by the number of chest or abdomen examinations determined from interviews and record searches. Implying that any dosimetry has been done is misleading. The computation of radiation doses from external radiation exposures is extremely complex,[24, 60-63] and should have been treated with more care.

The reported dose-response curve is of little use since it treats all examinations in the years preceding leukemia diagnosis as equal. This is incorrect because the exposure in roentgens per x-ray varied over the years of possible exposure. It is incorrect to assume that an x-ray exposure in 1940 equaled one in 1950 and certainly not in 1964, the year of the US Public Health Service survey. X-ray units were being modified during the 1930s and 1940s to reduce skin exposures,[64] most frequently by adding extra filtration. A typical skin exposure from a radiographic chest examination in the 1930s was 0.185R[24] in 1964 was 0.045R,[58] and in 1972-74 was 0.023R.[65] If proper dosimetry were possible for the tri-state data, the ordering of the dose categories might very well change. A change in the *shape* of the dose-response function for radiation-induced breast cancer was recently reported when varying exposures over the years 1930-1954 and other dosimetric factors were accounted for in the analysis.[24] The statement that "the use of other contrasts would not affect the conclusion concerning the shape of the curve" *is not justified.*

It should also be stressed that exposure to the skin is not related to risk of leukemia in any simple fashion. Active bone marrow is the critical organ for radiation-induced leukemia induction. Bone marrow doses need to be determined from skin exposures [60, 62, 63] for any dose-effect relationship to be at all meaningful.

It is also not clear how the 0.167R value for chest exposure was determined. The USPHS references,[58, 59] list 0.045R for a radiographic chest examination and 0.504R for a photofluorographic examination.

Finally, in the interest of thoroughness, it might be mentioned that the unit "centirad" means 1/100th rad and not 100 rad as used by Bross et al.

TABLE 5—2×2 Contingency Table Analyses of Heart Disease Versus Leukemia within Age and Dose Classes

Age	Dose (rad)	Leukemia	Heart Disease +	Heart Disease −	Odds Ratio	P
65+	<1	+	9	14	2.19	.20
		−	5	17		
	1-5	+	9	19	2.01	.24
		−	4	17		
	5-10	+	7	9	1.56	.41
		−	5	10		
	10-20	+	10	13	0.77	.62
		−	4	4		
	20+	+	5	6	0.83	.55
		−	1	1		
	Summary*				1.56	.13
45-64	<1	+	5	12	4.08	.05
		−	5	49		
	1-5	+	10	14	28.57	<.001
		−	1	40		
	5-10	+	4	5	2.06	.32
		−	7	18		
	10-20	+	1	13	0.23	.79
		−	4	12		
	20+	+	5	5	undef	.05
		−	0	7		
	Summary*				3.71	<.001
15-44	<1	+	1	26	0.90	.53
		−	2	47		
	1-5	+	0	2	undef	.70
		−	1	6		
	5+	+	1	1	5.00	.50
		−	1	5		
	Summary*				1.21	.42

*Adjusted for radiation exposure.[53, 54]

Discussion

The tri-state leukemia survey has made contributions to radiation carcinogenesis in the past by confirming the leukemia risk of prenatal x-ray exposure,[66] by suggesting a possible risk associated with preconception irradiation,[66] by suggesting that diagnostic irradiation may play a small role in adult male leukemia,[3] and by emphasizing the possible existence of high risk groups who may be especially sensitive to radiation.[67] However, the current paper[1] stretches the data far beyond reasonable limits to produce unwarranted conclusions.

Although the data base for the tri-state survey was large, the "new statistical methodology" introduced by Bross, et al, depends on a model that is far too complex to be useful. Without the incorrect statistical manipulations employed by the authors, the analysis would produce estimates so imprecise as to be meaningless. The model also incorporates an indirect measure of dose effect, provocatively labeled the "proportion affected by radiation, " whose meaning is obscure. It is particularly confusing that this measure should not approach zero as dose approaches zero and that the "proportion affected" should be over 50 per cent for doses as low as 40 rad. It is doubtful that the model is a reasonable representation of the relationship between radiation dose and leukemia risk.

It is also questionable whether Bross, et al. fully appreciate the implications of their analysis. Contrary to their interpretation, the shape of the 'purported dose-effect curve implies that low-dose irradiation has less effect per t-ad than high dose irradiation and that linearity *overestimates* the risk of radiation exposure at low doses.

There may be a risk associated with every radiation exposure, and no exposure should be assumed free of harmful effects; however, society is not well served by exaggerating presumptive risks and excluding the possibility of benefit. Medical radiation exposure does contribute substantially to the total radiation dose received by the U.S. population, and we agree with Bross, et al, and others[68,69] that no medical x-ray should be performed needlessly. Unnecessary radiation exposure should be eliminated and ways to reduce radiation doses of medical procedures, without reducing clinical value, should be encouraged.[68] The Bross, et al, analysis,[1] however, does not indicate that the risk of low level radiation exposure is greater than currently accepted.[10,11]

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